Magnesium Supplementation in the Treatment of Diabetes

Numerous research reports and clinical commentaries regarding magnesium deficiency have appeared in recent years. Linkages between magnesium deficiency and insulin resistance, carbohydrate intolerance, accelerated atherosclerosis, dyslipidemia, hypertension, and adverse outcomes in pregnancies complicating diabetes have been observed or postulated. Direct effects of insulin on magnesium metabolism and transport have also been described. Clinical trial results, though limited, have drawn attention to the potential benefits of magnesium replenishment.

To assess the relevancy of these observations to diabetes research and practice, the American Diabetes Association sponsored a consensus conference on magnesium supplementation in the treatment of diabetes on 15–16 May 1992 in Philadelphia, PA. Eight experts in diabetes and related disorders heard 13 presentations from U.S. and European investigators respected in the field of magnesium metabolism and its impact on health and disease. The consensus panel was asked to answer the following five questions focusing on diagnostic and therapeutic issues regarding magnesium and diabetes:

1. What is the relationship between magnesium levels and disease?
2. Is there a magnesium abnormality in diabetes? If so, what is its importance?
3. Is magnesium deficiency a risk factor in diabetes?
4. Should magnesium levels be measured in people with diabetes? If so, how and when?
5. Should people with diabetes receive magnesium supplementation? What is the safety and efficacy of such supplementation?

The following consensus responses were then developed by the panel.

QUESTION 1: WHAT IS THE RELATIONSHIP BETWEEN MAGNESIUM LEVELS AND DISEASE?—Magnesium, the second most abundant intracellular cation, plays a key role in cellular metabolism. It is important for cardiac contractility and conductivity, neurochemical transmission, skeletal muscle excitability, and the maintenance of normal intracellular calcium, potassium, and perhaps sodium levels.

Magnesium is found primarily in bone and muscle tissue, with ~1% in extracellular fluid. Normal serum concentrations are 1.5–2.0 mEq/L. Magnesium is found in various foods but particularly good sources include liver, nuts, leafy green vegetables, legumes, and whole grains. The RDA for magnesium is 350 mg for men and 300 mg for nongravid women. Although it is estimated that only 30% of dietary magnesium is absorbed from the gut, and that the overall intake of dietary magnesium has declined during this century, magnesium deficiency as a result of inadequate dietary intake is unusual in the U.S.

There are three main causes of magnesium deficiency: excessive urinary losses (e.g., diuretic therapy, diabetic ketoacidosis), decreased intestinal absorption (e.g., severe diarrhea, small bowel resection), and decreased dietary intake (e.g., prolonged parenteral nutrition). Hypermagnesemia may develop in people with renal insufficiency; the levels of toxicity are not clearly defined, but central nervous system depression appears at levels of ~8–10 mEq/L.

Available data suggest that magnesium concentrations (both serum and intracellular) are decreased in a number of disease states including hypertension, diabetes, perinatel morbidity in diabetic pregnancies, arrhythmias, and congestive heart failure. Additionally, there are data relating magnesium deficiency to insulin resistance. Some investigators believe that diminished magnesium concentrations may underlie the "insulin-resistance syndrome."

Data relating magnesium deficiency to human disease are limited. Much of the data has been generated either in nonprimate animal models or in cross-sectional studies in humans involving hospitalized or clinic-based control groups. Carefully designed case control studies involving population-based control subjects, cohort studies, or clinical trials have not been performed. However, a small number of limited clinical trials have been performed examining the effect of magnesium replacement in the periinfarction period on ventricular arrhythmias and mortality. A recent metaanalysis by Teo et al. (1) suggests a beneficial effect of magnesium replacement in reducing postmyocardial infarction mortality. The studies encompassed by the metaanalysis did not focus on diabetic subjects, although there is no reason to believe that the outcome should be different in diabetic compared with nondiabetic subjects.

In the absence of prospective studies, it is possible that decreased magnesium levels may represent a marker or epiphenomenon rather than a cause of disease. In a number of areas, such as

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hypertension and diabetes, cross-sectional studies are sufficiently promising that more rigorous intervention-based studies in human subjects should be undertaken.

QUESTION 2. IS THERE MAGNESIUM ABNORMALITY IN DIABETES? IF SO, WHAT IS ITS IMPORTANCE? —Hypomagnesemia has been demonstrated in both insulin-dependent and non-insulin-dependent diabetic patients. Magnesium deficiency in diabetes is most likely the result of increased urinary magnesium losses secondary to chronic glycosuria. However, short-term improvement in glycemic control has not been shown to restore the serum magnesium level. Long-term studies may be needed to resolve this discrepancy.

The impact of magnesium deficiency on insulin secretion and insulin action is speculative. Limited clinical studies have suggested a strong association between magnesium deficiency and insulin resistance. However, it is doubtful that magnesium deficiency plays a primary role in the pathophysiology of the abnormal carbohydrate metabolism of diabetes.

Acute hypomagnesemia may develop in diabetic ketoacidosis. Serum magnesium may parallel serum potassium. Elevated or normal levels of both potassium and magnesium may be seen in diabetic ketoacidosis at the time of presentation. After appropriate fluid and insulin treatment, magnesium levels may fall acutely, similar to serum potassium.

A role for magnesium deficiency in the development of the chronic complications of diabetes has not been established. However, the impact of hypomagnesemia in the pregnant diabetic patient deserves special consideration. Although the importance of magnesium depletion in malformations or stillbirths has not been firmly established, the neonates of hypomagnesemic mothers are especially susceptible to severe hypomagnesemia, hypocalcemia, and tetany.

QUESTION 3: IS MAGNESIUM DEFICIENCY A RISK FACTOR FOR DIABETES? —Currently, it would be premature to conclude that magnesium deficiency is a risk factor for the development of diabetes. However, strong associations have been shown between magnesium deficiency and insulin resistance. No study has demonstrated a causal relationship between the two. Also, there is no conclusive evidence in humans that magnesium deficiency chronically impairs insulin secretion. Therefore, the following areas of research should be pursued:

1. Prospective studies are needed to determine whether serum magnesium concentrations or other indices of magnesium nutrition predict the development of diabetes in population groups known to be at high risk.

2. Prospective studies are needed in diabetic patients to determine whether magnesium deficiency increases the risk of such complications as cardiovascular disease, retinopathy, or nephropathy.

3. Randomized controlled trials are necessary to demonstrate convincingly whether supplementation with magnesium will decrease the incidence of diabetes and its complications.

QUESTION 4. SHOULD MAGNESIUM LEVELS BE MEASURED IN PEOPLE WITH DIABETES? IF SO, HOW AND WHEN? —Currently available technology severely limits our ability to detect magnesium deficiency. The only measurements available routinely are serum and urine magnesium. Serum magnesium measures only 0.3% of the total body magnesium, and may poorly reflect the magnesium content of various tissues. However, decreased serum magnesium levels do reflect a reduction in total-body magnesium content, except in circumstances of acute magnesium depletion, such as rapid diuresis or recent administration of aminoglycoside antibiotics. Thus, serum magnesium is a specific but insensitive measure of magnesium depletion. Techniques that may better reflect total-body magnesium, such as ion selective electrodes or phosphate NMR spectroscopy, are research based and are not generally available for clinical use.

Urine magnesium must be measured in a 24-h sample, because variable excretion rates throughout the day make shorter measurements unreliable. The usefulness of urine testing in the diabetic patient is further limited by the fact that glycosuria enhances magnesium excretion. A magnesium tolerance (retention) test may provide more useful information about total-body magnesium stores. This test requires the parenteral administration of a calculated dose of magnesium, followed by 24-h urine collection, with calculation of the percentage of the magnesium load retained.

Until accurate indices of magnesium deficiency are available, routine evaluation of the magnesium status of otherwise healthy individuals with diabetes is not recommended. Nevertheless, it is appropriate to measure the serum magnesium in certain patients especially at risk of magnesium deficiency. These include patients with congestive heart failure or acute myocardial infarction, ketoacidosis, ethanol abuse, long-term parenteral nutrition, potassium or calcium deficiency, chronic use of certain drugs (e.g., diuretics, aminoglycosides, or digoxin), or pregnancy.

QUESTION 5. SHOULD PEOPLE WITH DIABETES RECEIVE MAGNESIUM SUPPLEMENTATION? WHAT IS THE SAFETY AND EFFICACY OF SUCH SUPPLEMENTATION?— Although considerable evidence has been published associating magnesium defi-

ciency with insulin resistance, diabetes, and hypertension, well-designed prospective studies demonstrating safety and beneficial results of magnesium replacement therapy have not been performed. Adequate dietary magnesium intake can generally be achieved by a nutritionally balanced meal plan as recommended by the American Diabetes Association.

Immediate beneficial effects from intravenous magnesium administration in the acute periinfarction period owing to a reduction of cardiac arrhythmias and of short-term postinfarction mortality have been demonstrated. Because myocardial infarction is the cause of death in most diabetic patients, magnesium administration to reduce peri-infarction mortality should be considered. A more complete evaluation of magnesium therapy in acute myocardial infarction will be forthcoming from clinical trials in progress.

In the preceding section, patients at high risk of magnesium deficiency were identified. In such patients documented with hypomagnesemia, oral magnesium chloride of dependable potency and bioavailability should be administered until such time as the serum magnesium level is normalized or the condition producing the hypomagnesemia is reversed. In patients with renal insufficiency and diminished glomerular filtration, oral magnesium replacement therapy must be carefully monitored because of the risk of hypermagnesemia. The risk-benefit ratio of such therapy should be weighed before initiating treatment.

The panel recommends that patients with diabetes at increased risk of magnesium deficiency as described above, but in whom such deficiencies cannot be demonstrated by clinically available tests, *not* receive magnesium supplementation. Investigational efforts that use newer technologies (e.g., NMR spectroscopy, ion selective electrodes) for demonstrating magnesium deficiency, which are presently unavailable in routine clinical practice, have suggested a high prevalence of such deficiencies in non-insulin dependent diabetes. Whether the results of these studies can be extended to the entire population of non-insulin dependent diabetes patients or only to selected patients remains unknown and therefore the benefit of treatment is uncertain.

CONCLUSION—In conclusion, the weight of experimental data presented to the consensus panel suggests that magnesium deficiency may play a role in insulin resistance, carbohydrate intolerance, and hypertension. Serum magnesium levels, although readily available, are relatively insensitive assessments of magnesium deficiency. The implementation of newer ion selective electrodes or phosphate NMR assays for ionized or free intracellular magnesium may extend our understanding of magnesium deficiency. However, based on available data, only diabetic patients at high risk of hypomagnesemia should have total serum magnesium assessed, and such levels should be repleted only if hypomagnesemia can be demonstrated.

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References

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